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Original Article

Objective sleep, a novel risk factor for alterations in kidney function: the CARDIA study

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ABSTRACT

Objective: To determine the association between objectively measured sleep and 10-year changes in estimated glomerular filtration rate (eGFR).
Methods: From 2003 to 2005, an ancillary sleep study was conducted at the Chicago site of the Coronary Artery Risk Development in Young Adults (CARDIA) study. Community-based black and white adults (aged 32–51 years) wore a wrist actigraph for up to six nights to record sleep duration and fragmentation. Sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI). Participants without history of cardiovascular or chronic kidney diseases, proteinuria, or hypertension at the 2000–2001 CARDIA examination were followed over 10 years ($n = 463$). eGFR was estimated from serum creatinine ($eGFR_{Cr}$) at the 2000–2001, 2005–2006, and 2010–2011 CARDIA examinations, whereas cystatin-C-estimated eGFR ($eGFR_{Cys}$) was measured at the 2000–2001 and 2005–2006 examinations. Generalized estimating equation regression and linear models estimated the associations of each sleep parameter with changes in $eGFR_{Cr}$ and $eGFR_{Cys}$, controlling for cardiovascular and renal risk.
Results: Sleep parameters were not related to 5-year change in $eGFR_{Cys}$. However, each 1 h decrease in sleep duration was significantly associated with a 1.5 mL/min/1.73 m^2 higher $eGFR_{Cr}$ [95% confidence interval (CI), 0.2–2.7], and each one-point increase in PSQI was significantly associated with a 0.5 mL/min/1.73 m^2 higher $eGFR_{Cr}$ (95% CI, 0.04–0.9) over 10 years.
Conclusion: In this community-based sample, shorter sleep and poorer sleep quality were related to higher kidney filtration rates over 10 years.

1. Introduction

Poor kidney function, as measured by estimated glomerular filtration rate (eGFR) [1,2] and restricted and poor quality sleep are novel risk factors for cardiovascular disease (CVD) and mortality [3–5]. However, the literature on the relationship between sleep and kidney disease development is scant. A review proposed that sleep disturbances may contribute to chronic kidney disease (CKD) development either indirectly through its influences on diabetes, obesity and hypertension, or directly through the sympathetic nervous system and renin–angiotensin–aldosterone system [6]. Obstructive sleep apnea may also contribute directly to the development of CKD because it is associated with glomerular hyperfiltration, proteinuria, and endothelial dysfunction [6,7]. Only one study to date has investigated the relationship between sleep and kidney function among healthy adults without CKD. Results revealed that short self-reported sleep (<5 h) was associated with increased incidence of proteinuria in a large sample of young to middle-aged Japanese adults [8].

The aim of the present study was to determine whether objectively assessed sleep duration and fragmentation, and self-reported sleep quality are associated with change in kidney function. Certain sex and race groups may be at greater risk for kidney dysfunction because the severity of disrupted and restricted sleep varies by these groups [9]. Therefore, the second aim was to determine whether the relationships between sleep and kidney function vary by sex and race.

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2. Methods

2.1. Study sample and design

From 1985 to 1986, the CARDIA study recruited 18–30-year-olds balanced by age (18–24, 25–30 years), race (self-reported black or white), sex, and education level (<high school, ≥high school) from four US sites. Participants were re-examined approximately every 2–5 years with the latest examination occurring 25 years after baseline (2010–2011). Methodological information for the CARDIA study is provided elsewhere [10]. At the Chicago site, an ancillary CARDIA Sleep Study was conducted in 2003–2005 among participants who were not pregnant during the CARDIA year 15 (2000–2001) examination. Eligible participants who gave written consent ($n = 670$; 82%) wore actigraph watches and completed self-reported sleep measures at two separate measurement periods one-year apart.

For the present analysis, CARDIA Sleep Study participants were excluded if they had one or more of the following conditions at the year 15 (2000–2001) examination: high blood pressure, heart problems, diabetes mellitus, peripheral vascular disease, kidney problems, stroke or transient ischemic attack, blood clot in leg veins or lungs requiring blood-thinning medicine, CKD (eGFR <60 mL/min/1.73 m^2), clinical proteinuria (albumin/creatinine ≥30 mg/mmol in a spot urine sample), high systolic (≥140 mmHg) or diastolic blood pressure (≥90 mmHg), and hypertension medication use. The final sample size was 463 at baseline. For this analysis, baseline was defined as the year 15 examination, and 5-year and 10-year follow-up as the CARDIA year 20 and 25 examinations, respectively. The flow of the study design is presented in Fig. 1. All institutional review boards reviewed and approved of the study protocol.

2.2. Measurement of eGFR

All participants underwent a 12 h fasting blood draw during the early to mid-morning at each examination (baseline, 5-year, and 10-year follow-up). GFR was estimated from two different markers, cystatin C and serum creatinine. Two markers were evaluated because GFR estimated from serum creatinine can vary in accuracy due to influence from muscle mass and diet; therefore estimation with cystatin C is a valuable alternative. However, cystatin C levels were assayed only at baseline and 5-year follow-up. Thus, estimates of 10-year changes were not possible. Cystatin C levels were measured by nephelometry using the N Latex cystatin C kit (Dade Behring, now Siemens). Serum creatinine concentrations at each examination were measured by nephelometry according to National Institute of Standards and Technology standards (Linco Research, Inc., St Louis, MO, USA) [11]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to compute eGFR from serum creatinine (eGFR$_{Cr}$) [12]. The CKD-EPI equation is superior to the Modification of Diet in Renal Disease Study equation for risk prediction, and estimating GFR values >60 mL/min/1.73 m^2 [13,14]. Values of eGFR were measured continuously as well as categorically into percentage change in eGFR from baseline to 5-year follow-up for estimates based on cystatin C (eGFR$_{Cys}$), and 10-year follow-up for estimates based on serum creatinine (≥3% decrease; –2.99% to 2.99% change, and ≥3% increase).

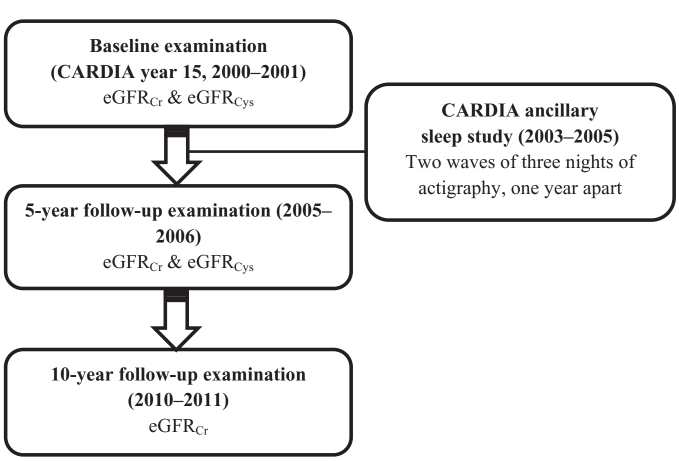

Fig. 1. Study design. CARDIA, Coronary Artery Risk Development in Young Adults Study. eGFR$_{Cr}$, glomerular filtration rate estimated from serum creatinine; eGFR$_{Cys}$, glomerular filtration rate estimated from cystatin C.

2.3. Sleep measures

Sleep parameters were procured from averages of up to six nights of wrist actigraphy data (Actiwatch-16, Mini-Mitter, Inc., Bend, OR, USA). Average sleep duration and sleep fragmentation were computed from two waves of data collection occurring one year apart from 2003 to 2005. Each wave consisted of three consecutive days of recording. Sensitive omnidirectional accelerometers within each actigraph measured wrist activity in 30 s epochs. Sleep duration and sleep fragmentation were calculated using validated algorithms provided by the manufacturer's software package. Sleep duration was defined as time from sleep onset to final awakening, subtracting time spent awake during that period. Sleep fragmentation scores, or a measure of the restlessness of sleep, were estimated by summing the percentage of movement time with the percentage of time spent immobile for ≤1 min. A previous report found high continuity in the values recorded between the two waves for sleep duration [15]. Further information on the methods used in the CARDIA Sleep Study have been described [9]. Sleep quality was also assessed using the Pittsburgh Sleep Quality Index (PSQI) [16]. The PSQI is a validated and reliable instrument that provides a measure of global sleep quality over the previous month. Higher scores indicate poorer sleep quality with a clinical cut-off of >5 suggesting moderate-to-severe sleep difficulties.

2.4. Other measurements

The following measurements were made at baseline, 5-year follow-up, and 10-year follow-up. Smoking status was classified as current vs former/never. Physical activity was assessed with the CARDIA Physical Activity History Questionnaire, which has acceptable psychometric properties and measures the frequency and duration over the previous year of engagement in 13 physically based activities [17]. Alcohol use was defined as the average number of alcoholic beverages consumed per week.

Body mass index was calculated as weight in kilograms divided by height in meters-squared. Nephelometry was used to assay high sensitivity C-reactive protein (hs-CRP) from plasma [18]. Low-density lipoprotein (LDL) levels were calculated with the Friedewald equation after total cholesterol and triglycerides were measured enzymatically with the Abbott Spectrum diagnostic system using the Trinder-type method for lipoproteins [19,20]. The Center for Epidemiologic Studies Depression scale (CES-D) was used to measure symptoms of depression [21]. The Berlin Questionnaire ascertained sleep apnea risk through a set of three risk factor categories: frequent daytime sleepiness; loud, persistent snoring or nocturnal breathing pauses; and either having hypertension or body mass index (BMI) >30 kg/m^2 [22]. Reporting positively to two or more categories is indicative of high risk for sleep apnea. However, participants with hypertension were excluded from the present analyses, and baseline BMI and change in BMI were separately controlled; thus, daytime sleepiness and frequent snoring were the sole symptoms included in multivariate analyses.

2.5. Statistical analysis

Sample characteristics in relation to each sleep parameter were computed with Pearson correlation coefficients for continuous variables and one-way ANOVA models for categorical variables.

To measure the association between each sleep parameter and $eGFR_{Cys}$ from baseline to 5-year follow-up, generalized linear models were used while controlling from baseline covariates in a sequence of nested models. Model 1 included the sleep parameter, age, sex, race, income, and education. Model 2 adjusted additionally for confounding factors, including depressive symptoms, smoking status, alcohol consumption, daytime sleepiness and frequent snoring. Model 3 further adjusted for potential intermediate factors, including physical activity, LDL and hs-CRP levels, BMI and change in BMI. Model 3 was considered to be potentially explanatory. hs-CRP and physical activity values were log-transformed to better approximate a normal distribution. The presence of non-linear associations was tested with the addition of quadratic terms. If the adjusted relationships were significant, then the association between sleep and percentage change in $eGFR_{Cys}$ (≥3% decrease; –2.99% to 2.99% change; and ≥3% increase) was also assessed with cumulative ordinal logit models adjusting for all covariates. These models were constructed to gauge any clinically significant changes in $eGFR_{Cys}$. Interaction terms were appended to model 3 to determine whether the relationships varied by race, sex, or race–sex groups. Significant interaction terms were followed by stratified analyses.

Generalized estimating equation (GEE) regression models were used to estimate the dependence of changes in $eGFR_{Cr}$, evaluated at three examinations over 10 years (2000–2001, 2005–2006, and 2010–2011) on each sleep parameter, after adjusting for the same sequence of nested covariate models, change in the covariates over time, and the correlation between the eGFR values at each examination year [23]. The regression estimate can be interpreted as the average change in eGFR over 10 years related to the sleep parameter. Separate, additional models were constructed to add interaction terms between the sleep parameter and each time point (5-year follow-up and 10-year follow-up) to estimate significant variation in the slope of the relationship between sleep and $eGFR_{Cr}$ over time compared to baseline (model 4a), and to add interaction terms between the sleep parameters and race, sex, and race–sex groups (model 4b). Due to repeated measurement of the participants over time, unstructured correlation structure was employed to take into account correlation among them to correct the standard error.

All non-missing pairs of data were used to estimate model parameters along with correlation structure. For data presentation purposes, sleep duration and PSQI scores were also included as categorical variables to provide more clinically meaningful cut-off points for interpretation. Sleep duration was categorized into four categories: <4.5 h; 4.5–5.99 h; 6–7.49 h; and ≥7.5 h. PSQI scores were categorized into a dichotomous variable using the clinical cut-off score of 5 [17]. Cumulative logit models controlling for all covariates were also analyzed to evaluate percentage change in $eGFR_{Cr}$ as associated with the sleep parameters. All regression coefficients were tested for significance at the 0.05 α-level using two-sided tests. Statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Participants

Eligible participants did not differ significantly from ineligible participants at the CARDIA Chicago site in age, sex, smoking status, alcohol use, and LDL levels. Ineligible participants (those with prior history of CVD, CKD proteinuria, and hypertension) were significantly more likely to be black, have less education, less income, higher hs-CRP levels, higher BMI, engage in less physical activity, and report more depressive symptoms (data not presented).

3.2. Descriptive characteristics

In Table 1, characteristics of the sample at baseline examination are displayed along with each characteristic's association with sleep duration, fragmentation score, and PSQI score. On average, the study participants slept 6.1 h [standard deviation (SD), 1.1]. The average sleep fragmentation score was 19.2% (SD, 8.1) and mean sleep quality was borderline poor (mean, 5.6; SD, 2.7).

In Fig. 2 the changes in $eGFR_{Cr}$ over 10-year follow-up in the total sample is represented along with changes in $eGFR_{Cr}$ by race–sex groups. $eGFR_{Cr}$ diminished in the total sample and across all race–sex groups over the follow-up period. Whites had lower $eGFR_{Cr}$ values than blacks at each clinical examination. Black women had the highest $eGFR_{Cr}$ values at each time-point. Over the follow-up period, 11.9% ($n = 55$) of the sample did not provide values for $eGFR_{Cr}$ at one or both follow-up examinations. This attrition did not differ by age, sex, race, income, education, BMI, any of the sleep parameters, or baseline $eGFR_{Cr}$ (data not presented).

3.3. Sleep duration and changes in $eGFR_{Cys}$ and $eGFR_{Cr}$

Table 2 shows the association between each sleep parameter and changes in $eGFR_{Cys}$ over 5 years. Table 3 shows the association between each sleep parameter and changes in $eGFR_{Cr}$ over 10 years. In the unadjusted and adjusted models of $eGFR_{Cys}$, sleep duration was not significantly associated with $eGFR_{Cys}$. In the unadjusted model of $eGFR_{Cr}$, each 1 h increase in sleep duration was associated with a 2.9 mL/min/1.73 m^2 decrease in $eGFR_{Cr}$. After adjusting for confounders in models 1 and 2, the association attenuated but remained significant. The point estimate did not diminish and remained significant with adjustment for potential mediators in model 3. The sleep × time interaction in model 4a revealed that the relationship between sleep duration and $eGFR_{Cr}$ did not significantly vary over time. There were no significant interactions with race, sex, or race–sex groups ($P > 0.05$). The test for a quadratic association was also not significant. Therefore, each 1 h increment in sleep duration was significantly associated with a 1.5 mL/min/1.73 m^2 decrease in $eGFR_{Cr}$ over 10-year follow-up, or alternatively each 1 h decrement in sleep duration was significantly associated with a 1.5 mL/min/1.73 m^2 increase in $eGFR_{Cr}$ over 10-year follow-up. Table 4 further clarifies this association by displaying sleep duration categorically. The fully adjusted model revealed that shorter sleep was associated, though not significantly, with increasing eGFR in a graded fashion. Cumulative logit models were analyzed to understand whether this association is related to clinically meaningful percent change in eGFR (Table 5). A 1 h increase in sleep duration was associated with 17% greater odds of a ≥3% decrease in eGFR, though the association did not reach statistical significance.

3.4. Sleep fragmentation and changes in $eGFR_{Cys}$ and $eGFR_{Cr}$

In the unadjusted and adjusted models of $eGFR_{Cys}$, a 10% higher sleep fragmentation score was not significantly associated with change in $eGFR_{Cys}$ over 5 years (Table 2). In the unadjusted model of $eGFR_{Cr}$, a 10% increment in sleep fragmentation was significantly associated with increases in $eGFR_{Cr}$ over 10 years, but adjustment for sociodemographic factors rendered the estimate non-significant (Table 3). However, there were separate, fully adjusted (model 4b) significant interactions of sleep fragmentation with sex ($P = 0.02$), and race ($P = 0.02$). For men there was a 0.2 mL/min/

Table 1
Baseline characteristics of the CARDIA sleep study sample and their associations with sleep duration, fragmentation and quality[a].

Variable	Total sample		Sleep duration		Sleep fragmentation		PSQI	
	N	Mean (SD) or %	Mean (SD) or *r*	*P*	Mean (SD) or *r*	*P*	Mean (SD) or *r*	*P*
Age (years)	463	39.9 (3.7)	0.06	0.19	–0.14	0.003	–0.04	0.40
Sex				<0.001		<0.001		0.10
Men	210	45.4	5.8 (1.2)		21.0 (8.5)		5.4 (2.5)	
Women	253	54.6	6.4 (0.9)		17.7 (7.4)		5.8 (2.9)	
Sex-race				<0.001		<0.001		<0.001
White women	147	31.8	6.7 (0.8)		16.3 (6.2)		5.3 (2.5)	
White men	132	28.5	6.2 (0.9)		19.3 (7.3)		5.0 (2.2)	
Black women	106	22.9	5.9 (0.8)		19.7 (8.5)		6.4 (3.2)	
Black men	78	16.8	5.2 (1.3)		24.0 (9.4)		6.0 (2.8)	
Income				<0.001		<0.001		<0.001
<$16,000	23	5.0	5.3 (1.4)		23.1 (7.6)		8.1 (4.3)	
$16,000–34,999	54	11.8	5.8 (1.2)		23.2 (10.8)		6.8 (2.7)	
$35,000–74,999	157	34.3	6.0 (1.1)		19.9 (8.4)		5.7 (2.7)	
≥$75,000	224	48.9	6.4 (0.8)		17.3 (6.4)		5.0 (2.3)	
Education				<0.001		<0.001		<0.001
<High school	87	18.8	5.7 (1.4)		22.9 (9.6)		6.6 (3.1)	
High school degree	255	55.1	6.1 (1.0)		18.9 (7.7)		5.6 (2.7)	
Some college or higher	121	26.1	6.4 (0.8)		17.3 (6.7)		5.0 (2.3)	
Smoking status				0.004		<0.001		0.02
Non-smoker	370	80.1	6.2 (1.0)		18.4 (7.4)		5.4 (2.6)	
Current smoker	92	19.9	5.8 (1.3)		22.7 (9.6)		6.2 (2.9)	
Alcohol (mL/day)	461	10.8 (19.7)	–0.02	0.74	0.09	0.05	0.03	0.51
BMI (kg/m^2)	462	27.6 (5.9)	–0.18	<0.001	0.16	<0.001	0.22	<0.001
Log_physical activity	463	5.5 (1.1)	–0.02	0.71	–0.11	0.02	–0.01	0.89
CES-D	460	8.1 (7.3)	–0.09	0.04	0.11	0.02	0.41	<0.001
Log CRP	450	0.2 (1.2)	–0.04	0.43	0.15	0.002	0.13	0.01
LDL	454	114.9 (32.0)	0.02	0.64	0.02	0.60	–0.07	0.12
BQ-snore				0.36		0.06		0.03
Non-snorer	407	87.9	6.1 (1.0)		18.9 (7.4)		5.5 (2.7)	
Snorer	56	12.1	6.0 (1.1)		21.9 (11.7)		6.4 (2.7)	
BQ-tiredness				0.28		0.73		<0.001
Not tired	329	71.1	6.0 (1.0)		19.1 (8.0)		5.0 (2.5)	
Tired	134	28.9	6.2 (1.1)		19.4 (8.3)		7.1 (2.7)	
eGFR$_{Cr}$								
Baseline	463	103.1 (15.8)	–0.18	<0.001	0.15	0.002	0.14	0.006
5-year follow-up	389	96.4 (15.2)	–0.22	<0.001	0.16	0.001	0.24	<0.001
10-year follow-up	319	95.3 (15.6)	–0.23	<0.001	0.14	0.01	0.22	<0.001

Abbreviations: BMI, body mass index; BQ, Berlin Sleep Questionnaire; CES-D, Center for Epidemiological Studies Depression scale; eGFR$_{Cr}$, estimated glomerular filtration rate as estimated with serum creatinine; LDL, low-density lipoprotein; log CRP, log-normalized C-reactive protein; PSQI, Pittsburgh Sleep Quality Index.
[a] Associations between categorical factors and continuous sleep measures were conducted with one-way analyses of variance [displayed as means (standard deviations) with *P*-values], and associations between continuous factors and continuous sleep measures were conducted with Pearson's correlation coefficients (displayed as *r* with *P*-values).

1.73 m^2 increase in eGFR$_{Cr}$ associated with each 10% increment in sleep fragmentation (95% CI, 0.1, 0.4; $P = 0.01$). There was no association in women (eGFR$_{Cr}$ estimate, –0.2; 95% CI, –0.4, 0.1; $P = 0.17$). For whites there was a 0.2 mL/min/1.73 m^2 increase in eGFR$_{Cr}$ associated with each 10% increment in sleep fragmentation (95% CI, 0.02, 0.35; $P = 0.03$), but there was no significant association for blacks (eGFR$_{Cr}$ estimate, –0.05; 95% CI, –0.3, 0.2; $P = 0.66$).

3.5. Sleep quality and changes in eGFR$_{Cys}$ and eGFR$_{Cr}$

The unadjusted and adjusted relationships between PSQI score and 5-year change in eGFR$_{Cys}$ were non-significant (Table 2). However, the crude relationship between PSQI scores and 10-year change in eGFR$_{Cr}$ indicated a statistically significant increase of 1.2 mL/min/1.73 m^2 (Table 3). In the fully adjusted model (model 3) each one-point increment in PSQI score was related to a 0.5 mL/min/1.73 m^2 increase in eGFR$_{Cr}$ ($P = 0.03$). The relationship did not significantly vary as a function of time (model 4a). In Table 4, poor sleepers (PSQI score >5) had a significant increase in eGFR$_{Cr}$ of 5.2 mL/min/1.73 m^2 over 10 years in the unadjusted model. However, in model 2 the point estimate became statistically non-significant and remained so in model 3. There were no significant interactions with race, sex, or race–sex groups. The cumulative logit model that assessed the association between PSQI scores and clinically meaningful percentage change in eGFR$_{Cr}$ over 10 years revealed that a one-point increase in PSQI score was significantly associated with a 13% greater odds of having a ≥3% increase in eGFR$_{Cr}$ relative to baseline eGFR$_{Cr}$.

4. Discussion

In this community-based cohort of young-to-middle aged black and white adults without a history of CVD, CKD, proteinuria, or hypertension, shorter actigraphy-measured sleep duration and poorer reported sleep quality were associated with statistically significant increases in eGFR$_{Cr}$ over a 10-year follow-up. The rate of change in eGFR$_{Cr}$ as a function of sleep duration or sleep quality did not vary over time. The increases were modest in magnitude. The largest increases in eGFR$_{Cr}$ were associated with <4.5 h of sleep, or a PSQI score >5, on average. Nonetheless, the relationship between sleep quality and eGFR$_{Cr}$ was clinically meaningful such that a one-point increase in PSQI score was associated with a 13% greater odds of having a ≥3% increase in eGFR$_{Cr}$ over 10 years. Sleep fragmentation was not associated with changes in eGFR$_{Cr}$ in the overall sample; however, 10% increments in sleep fragmentation among men and whites were significantly associated with small increases in eGFR$_{Cr}$.

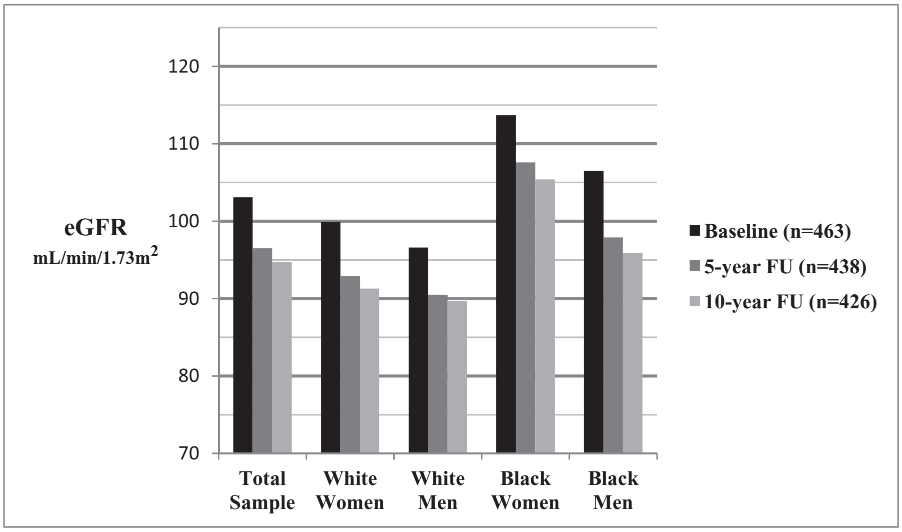

Fig. 2. Glomerular filtration rate (means) estimated with serum creatinine across each clinical examination by race–sex groups. eGFR, estimated glomerular filtration rate; FU, follow-up.

There were no significant associations between any of the sleep parameters and change in GFR from baseline to 5-year follow-up when GFR was estimated with cystatin C.

The relationships between sleep duration and 10-year change in $eGFR_{Cr}$ were statistically meaningful after adjustment for many relevant confounders. Adjustment for potential mediators did not change the estimates substantially, suggesting that there may be other factors that play larger roles. The direction of the relationships is counter to the general decreases in $eGFR_{Cr}$ in the overall sample as well as counter to the declines found in the literature that have been argued to occur with normal aging, starting around ages 30–40 years [24]. High levels of eGFR are an early predictor of diabetes and hypertension [25,26], associated with increasing levels of pre-diabetes and pre-hypertension in the general population [27], and are associated with higher incidence rates of coronary heart disease and mortality [5]. We hypothesize, based on extant studies, that poor or short sleep may increase sympathetic nervous system activity [28], blunt normal falls in blood pressure that occur during sleep [29,30], and impair metabolic regulation [28,31]. These changes, in turn, may then increase eGFR to abnormally high levels, hence increasing the risk for glomerular hypertension, renal injury, and the development of CKD and CVD risk factors. Unfortunately there is no universal definition of what constitutes a clinically important raw increase in eGFR or what level indicates a diagnosis of a

Table 2
Linear association between sleep duration, fragmentation, quality, and change in glomerular filtration rate from baseline to 5-year follow-up as estimated with cystatin C[a].

Predictor	Unadjusted			Model 1			Model 2			Model 3		
	Est	*t*	*P*	Est	*t*	*P*	Est	*t*	*P*	Est	*t*	*P*
Sleep duration (per hour increase)	0.44	1.2	0.23	0.47	1.1	0.25	0.49	1.2	0.24	0.33	0.8	0.40
Fragmentation (per 10% increase)	–0.1	–1.5	0.15	–0.1	–1.7	0.09	–0.08	–1.6	0.11	–0.04	–0.9	0.36
PSQI (per 1-point increase)	–0.1	–0.7	0.46	–0.03	–0.2	0.82	–0.01	–0.1	0.94	0.12	0.8	0.45

Model 1: age, sex, race, income and education.
Model 2: Model 1 + depressive symptoms, sleep apnea risk, alcohol use, smoking status.
Model 3: Model 2 + physical activity, body mass index and change in body mass index, C-reactive protein level, low-density lipoprotein level.
Abbreviations: CI, confidence interval; Est, estimate of regression coefficient; PSQI, Pittsburgh Sleep Quality Index.
[a] Estimated glomerular filtration rate measured as mL/min/1.7 m^2.

Table 3
Generalized estimating equation models for association between sleep duration, fragmentation, quality, and glomerular filtration rate estimated with serum creatinine[a].

Predictor	Unadjusted		Model 1		Model 2		Model 3		Model 4a	
	Est	95% CI	Est	95% CI	Est	95% CI	Est	95% CI	Est sleep × time[b]	95% CI
Sleep duration (per hour increase)	–2.9	–1.6, –4.1	–1.7	–0.5, –2.9	–1.5	–0.3, –2.7	–1.5	–0.2, –2.7	–0.1	–1.5, 1.3
Fragmentation (per 10% increase)	0.3	0.1, 0.4	0.1	–0.1, 0.2	0.1	–0.1, 0.2	0.03	–0.1, 0.2	0.1	–0.1, 0.2
PSQI (per 1-point increase)	1.2	0.7, 1.7	0.6	0.2, 1.1	0.6	0.2, 1.1	0.5	0.04, 0.9	0.5	–0.1, 1.1

Model 1: age, sex, race, income and education.
Model 2: model 1 + depressive symptoms, sleep apnea risk, alcohol use, smoking status.
Model 3: model 2 + physical activity, body mass index, change in body mass index, C-reactive protein level, low-density lipoprotein level.
Model 4a: model 3 + interaction between sleep parameter and time.
Abbreviations: CI, confidence interval; Est, estimate of regression coefficient; PSQI, Pittsburgh Sleep Quality Index.
[a] Estimated glomerular filtration rate measured as mL/min/1.73 m^2.
[b] Estimate of the unstandardized regression coefficient for the interaction between the sleep parameter and time at 10-year follow-up.

Table 4
Generalized estimating equation models for association between categorized sleep duration, PSQI scores and GFR estimated with serum creatinine[a].

Predictor	Unadjusted			Model 1			Model 2			Model 3		
	Est	95% CI	*P*	Est	95% CI	*P*	Est	95% CI	*P*	Est	95% CI	*P*
Sleep duration (ref: ≥7.5 h)												
6.0–7.49	1.1	−3.0, 5.1	0.61	1.4	−2.1, 4.8	0.45	1.7	−2.0, 5.4	0.36	0.8	−2.8, 4.5	0.66
4.5–5.99	6.2	2.0, 10.5	0.004	4.3	0.5, 8.0	0.03	4.4	0.4, 8.3	0.03	3.2	−0.8, 7.2	0.11
<4.5	11.0	4.8, 17.2	<0.001	7.1	1.2, 12.9	0.02	6.3	0.2, 12.4	0.04	5.7	−0.5, 11.9	0.07
PSQI (ref: ≤5)												
>5	5.2	2.6, 7.8	<0.001	2.5	0.3, 4.7	0.03	2.1	−0.2, 4.4	0.08	1.8	−0.5, 4.0	0.12

Model 1 = age, sex, race, income and education.
Model 2 = Model 1 + depressive symptoms, sleep apnea risk, alcohol use, smoking status.
Model 3 = Model 2 + physical activity, body mass index, change in body mass index, C-reactive protein level, low-density lipoprotein level.
Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; Est, Estimate of regression coefficient; PSQI, Pittsburgh Sleep Quality Index.
[a] Estimated glomerular filtration rate measured as mL/min/1.73 m^2.

clinically high GFR [32]. In a community-based study of 99,140 adults from Japan, clinically relevant hyperfiltration levels at ages 30–39 and 40–49 years were 108 and 103 mL/min/1.73 m^2 for men, respectively, and 116 and 106 mL/min/1.73 m^2 for women, respectively [27]. It is uncertain whether these rates would generalize to white and black Americans; however, if these rates did translate, then in the present sample, black women on average had borderline hyperfiltration levels of eGFR$_{Cr}$ at 5-year and 10-year follow-up. In future investigations, diagnostic criteria for eGFR hyperfiltration should be determined along with the relationship between chronic sleep restriction and renal changes in the general population.

The present study is the first known investigation of the association between objectively measured sleep, reported sleep quality, and markers of renal functioning over a long follow-up period in an ethnically diverse community sample with no history of CVD or CKD. Nonetheless, several limitations deserve mention. First, the gold standard for identifying sleep – polysomnography – was not used in the present study. However, sleep duration is not well measured by polysomnography because it likely causes deviations from usual sleep habits due to the requirement that a technician set it up and it is somewhat invasive. Estimates of sleep continuity parameters from wrist actigraphy are consonant with polysomnography estimates [33]. Second, since polysomnography was not used in the present study, there is a possibility that sleep disorders, such as obstructive sleep apnea or restless legs syndrome, could have altered estimations of the independent and dependent variables (sleep parameters and GFR). Third, the generalizability of the results may be lessened due to the small size of the sample, inclusion of only two race/ethnic groups, narrow age range in early middle age, and its restriction to one geographical region. However, few studies have both objective sleep measurement and longitudinal follow-up. Therefore, the results still represent an important contribution to the field. Fourth, the observational design of the study precludes the ability to determine a causal link between sleep and renal filtration changes, and there remains the possibility of residual confounding from unmeasured factors such as diet and stress. Fifth, estimations of GFR using serum creatinine can be inexact due to various factors that affect serum creatinine levels such as muscle mass, diet, and illness. Estimation of GFR using cystatin C at 10-year follow-up would have allowed for greater precision, and a better indication of the directionality of the relationships. Therefore, these results should be interpreted with caution. Lastly, objective and reported sleep were not measured during the year 15 examination (i.e. baseline), rather in between baseline and the 5-year follow-up. However, estimates of the linear relationships between sleep and eGFR$_{Cr}$ using 5-year follow-up data as the baseline assessment were similar to the present results (data not presented).

In summary, our results suggest that parameters of poor objective and self-reported sleep among relatively healthy individuals may be novel and early indicators of adverse changes in kidney functioning. To verify these relationships, confirmatory, large observational studies among natural short- and normal-duration sleepers are needed to understand further the mechanisms that underlie changes in GFR as measured by cystatin C alone or in combination with serum creatinine. Examples of these mechanisms might be fluctuations in plasma renin and aldosterone levels, sympathetic nervous system activity, metabolic regulation, and blood pressure alteration. Longer-term studies are also required to ascertain whether increases in eGFR related to sleep are associated with poor kidney functioning and renal injury. There is also work needed in assessing the role of sleep in renal functioning among different patient groups. No known studies have investigated the nature of the relationship between sleep and the development of renal insult among patients with primary or comorbid insomnia, periodic limb movement disorder, or among naturally short or long sleepers. Early detection of sleep disturbances and disorders among patients already

Table 5
Proportional odds model of the association of sleep duration, fragmentation, and quality on percentage change in GFR estimated by serum creatinine over 10 years[a].

Predictor	Unadjusted		Model 1		Model 2		Model 3	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Sleep duration[b] (per hour increase)	0.80	0.64, 0.99	0.79	0.62, 1.02	0.78	0.60, 1.01	0.83	0.64, 1.08
Fragmentation[c] (per 10% increase)	1.01	0.98, 1.04	1.02	0.99, 1.05	1.02	0.99, 1.05	1.02	0.99, 1.05
PSQI[c] (per 1-point increase)	1.09	1.01, 1.17	1.10	1.02, 1.19	1.13	1.03, 1.24	1.13	1.02, 1.24

Model 1: age, sex, race, income and education.
Model 2: model 1 + depressive symptoms, sleep apnea risk, alcohol use, smoking status.
Model 3: model 2 + physical activity, body mass index, change in body mass index, C-reactive protein level, low-density lipoprotein level.
Abbreviations: CI, confidence interval; GFR, glomerular filtration rate; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index.
[a] Estimated glomerular filtration rate measured as mL/min/1.73 m^2.
[b] Modeled on ≥3% decrease in estimated GFR. Reference group: participants with little to no percentage change and participants with ≥3% increase in estimated GFR combined.
[c] Modeled on ≥3% increase in estimated GFR. Reference group: participants with little to no percentage change and participants with ≥3% decrease in eGFR combined.

experiencing renal decline, or who have other CVD risk factors, may also be clinically beneficial and should be investigated.

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Conflicts of interest

Dr Lewis receives research funding unrelated to the submitted work from Novo Nordisk; Dr Glasser receives salary support from AMGEN to evaluate trials for treating elevated LDL-cholesterol.

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